REMARKS

Claim Status

Claims 1-20 and 33-44 are pending. Claims 33-44 are withdrawn by the Examiner as being directed to a non-elected invention.

Claim Amendment

Claim 13 is amended to end in a period.

Claim 21 is cancelled.

Claim Rejections

Rejection of Claim 13

Claim 13 is rejected under 35 U.S.C. §112, second paragraph, as being indefinite due to the absence of a period. Applicants amended Claim 13 as required by the Examiner.

Reconsideration and withdrawal are requested.

Rejection of Claim 21

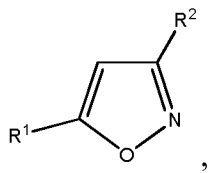
Claim 21 is rejected under 35 U.S.C. §102(b) as being anticipated by U.S. 5,814,627 ("Schwab").

Claim 21 is now cancelled.

Rejection of Claims 1-20

Claims 1-20 are rejected under 35 U.S.C. §103(a) as being unpatentable over Ferles *et al.*, "Synthesis and Reaction of Novel 1,3-Dipyridinyl-1,3-propabediones", Collect. Czech. Chem. Commun. (Vol. 55) (1990) ("Ferles") in view of Schwab.

Ferles teaches a compound of the following structural formula:



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having four combinations of values of variables R^1 and R^2:

$R^1 = R^2$ = 2-pyridine;

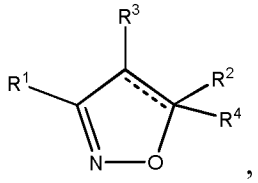
$R^1 = R^2$ = 3-pyridine;

R^1 = 2-pyridine; R^2 = 4-pyridine; and

R^1 = 4-pyridine, R^2 = 2-pyridine.

The Examiner stated that the difference between the instantly claimed compounds and the compounds of Ferles is in the saturation of the isoxazole compound.

Schwab teaches a compound of the following structural formula:



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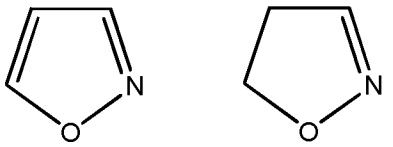
where the variable R^1 through R^4 are defined in Schwab, col. 1, l. 54 through col. 4, l. 4.

The Examiner stated that Schwab teaches a class of isoxazole compounds useful in the treatment of inflammation. The Examiner also stated that the saturation of isoxazole may vary. The Examiner further stated that it would have been obvious to one of ordinary skill in the art to "replace the generic isoxazole compound of Schwab," and that there is motivation to modify one ring system for another when there is expectation of similar pharmacological properties. (Office Action, p. 5.)

To the extent that the instant rejection is understood, the Examiner asserts that it would be obvious to one of ordinary skill in the art to select a compound of Ferles, and then to replace the isoxazole scaffold with the 4,5-dihydroisoxazole scaffold of Schwab, based on Schwab's teachings of compounds that, although substituted differently from those of Ferles, may include either the isoxazole or the 4,5-dihydroisoxazole scaffold.

Applicants respectfully disagree. Neither scientific analysis not legal precedent supports the Examiner's position.

Applicants will first address the scientific position taken by the Examiner. It is noted that Schwab teaches two different scaffolds, isoxazole and 4,5-dihydroisoxazole:



isoxazole , 4,5-dihydroisoxazole .

The Examiner's attention is respectfully directed at the cited isoxazole compounds of Ferles. Because isoxazole is fully unsaturated, and because all listed substituents are heteroaromatic pyridines, the central scaffold of Ferles' compounds is fully conjugated to each of its heteroaromatic substituent R^1 and R^2. In contrast, the 4,5-dihydroisoxazole scaffold of Schwab can never be fully conjugated to its substituents.

Thus, the compounds of Ferles exhibit π-electron delocalization over the entirety of the tri-cyclic molecule, unlike the 4,5-dihydroisoxazole compounds of Schwab. This alone is expected to translate into differences in size, shape, and electron density distribution between the fully conjugated molecules of Ferles and the 4,5-dihydroisoxazole molecules of Schwab, which cannot be fully conjugated. Therefore, absent supporting evidence, one of ordinary skill in the art would *not* expect that the physical, chemical and, therefore, pharmaceutical properties of a compound of Ferles will be retained if the conjugation is broken by replacing isoxazole with 4,5-dihydroisoxazole.

While Ferles is silent on the pharmaceutical properties of its compounds, Schwab itself provides no evidence of equivalence between fully conjugated and non-fully conjugated species. The Examiner is invited to consider the compounds listed in Table 1 of Schwab (col. 27 through 60). Not one of the listed compounds is an isoxazole conjugated to two heteroaryls. Therefore, Schwab cannot provide evidence of equivalence between isoxazole and 4,5-dihydroisoxazole in the context of heteroaromatic conjugated substituents. As such, one of ordinary skill in the art will *not* be motivated to select a compound of Ferles, and then to replace its isoxazole scaffold with the 4,5-dihydroisoxazole scaffold, based on the teachings of the cited references. Therefore, the compounds defined by Applicants' Claim 1 are non-obvious over the combination of Ferles and Shcwab.

The conclusion of non-obviousness reached above based on the scientific analysis of the cited references is also fully supported by the current Patent Law. The Examiner's attention is directed to a decision by the U.S. Court of Appeals for the Federal Circuit in Takeda Chemical v.

Alphapharm, 492 F.3d 1350, 83 U.S.P.Q.2D 1169 (C.A.F.C. 2007). The court of Takeda clearly delineated a two-step analysis of chemical obviousness:

> The [District] court properly concluded that Alphapharm did not make out a *prima facie* case of obviousness because Alphapharm failed to adduce evidence that compound b would have been selected as the lead compound and, even if that preliminary showing had been made, it failed to show that there existed a reason, based on what was known at the time of the invention, to perform the chemical modifications necessary to achieve the claimed compounds. (492 F.3d at 1362-1363)

Thus, in order to advance a *prima facie* case of chemical obviousness rejection, the Office must show that (1) there exists a compound, disclosed by a cited reference, that would have been selected as a "lead compound", and (2) there exists a reason to modify the selected "lead" compound in a manner necessary to obtain the claimed subject matter[1]. Furthermore, satisfying prongs (1) and (2), above, is not dispositive, but merely establishes a rebuttable *prima facie* case.

Applicants note that the court of Takeda confirmed a well-established principle of "chemical obviousness":

> [The] test for prima facie obviousness for chemical compounds is consistent with the legal principles enunciated in *KSR*. [...] Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound. (492 F.3d 1350 at 1356 and 1357)(*emphasis added*)[2]

The court of Takeda reaffirmed the principle annunciated In Re Grabiak, 226 USPQ 870 (CAFC 1985): it is improper to assume that different chemical structures would have the same properties, absent a teaching of equivalency in the prior art:

> Upon review of this history, we have concluded that generalization should be avoided insofar as specific chemical structures are alleged to be *prima facie* one

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[1] Applicants note that the C.A.F.C. opinion in Takeda was issued after the decision by the Supreme Court in KSR International Co. v. Teleflex Inc., 127 S. Ct. 1727 (2007).

[2] See also *In re Jones, 958 F.2d 347 (Fed. Cir. 1992)*; *Dillon, 919 F.2d 688*; *Grabiak, 769 F.2d 729*; *In re Lalu, 747 F.2d 703 (Fed. Cir. 1984)*, all cited by the court of Takeda.

> from the other. […] [I]n the case before us there must be adequate support in the prior art for the ester/thioester change in structure in order to complete the PTO's *prima facie* case and shift the burden of going forward to the applicant. (In Re Grabiak, 226 USPQ 870 at 872 (CAFC 1985)).

The court of In Re Grabiak further held:

> The Bollinger teaching of various heterocyclic rings containing two sulfur atoms or one oxygen and one sulfur atom, rings which are unlike any part of the Howe molecule, does not suggest the interchangeability of sulfur and oxygen in the ester moiety of the Howe molecule. (*Ibid.*)

Turning now to the facts of the present case, there is *no teachings of equivalence of the isoxazole and the 4,5-dihydroisoxazole scaffolds*, as explained above. Referring to Schwab's formula (I), there are *four substituents at three substitutable positions*, and there is *no teachings* in either reference that would direct one of ordinary skill in the art *to select the positions 3 and 5 on 4,5-dihydroisoxazole of Schwab for modifying the substitution* in a manner required to arrive at the compounds defined by Applicants' Claim 1. Finally, while in Ferles both substituents are *hetero*aryls, in Schwab, either R^1 or R^2 must be a di-*tert*-Butyl-phenyl, an aryl; and there is no teaching in either reference of the equivalence between the two types of substituents.

Applying the principles of Takeda and In Re Grabiak to the facts of this case, the Examiner's assertion of obviousness of Claim 1 over Ferles and Schwab amounts to the following steps, mandated by the current Patent Law, being obvious to one of ordinary skill in the art:

(1) Selecting the 4,5-dihydroisoxazole scaffold out of the group of isoxazole and 4,5-dihydroisoxazole scaffolds disclosed by Schwab.

(2) Selecting position 3 and 5 (out of positions 3, 4 and 5) on the 4,5-dihydroisoxazole for replacing the substituents with those of Ferles.

(3) Replacing the substituents of Schwab, at the positions selected in step (2) with the monocyclic six-member heteroaryl groups disclosed by Ferles.

Applicants submit that there is no teachings of equivalence of the isoxazole and the 4,5-dihydroisoxazole scaffolds, as explained above. There is no direction or motivation to select the position 3 and 5, out of positions 3, 4 and 5, on the 4,5-dihydroisoxazole on which the substituent will be replaced. Finally, there is no teachings of equivalence, in the context of the

4,5-dihydroisoxazole scaffold, of a combination of two heteroaryl substituents and a combination of substituents that must include one aryl (as in Schwab).

In other words, absent some structure-activity data indicating equivalence of the compounds of Schwab as defined in that reference and hypothetical compounds arrived at by the above-described series of steps, it is improper to assume that the hypothetical compounds would be pharmaceutically effective.

In view of the foregoing, reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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